What hasn’t been tried in a caudal?

Torrey Lynch MD CPT MC

(my first power pt presentation)

Why are caudals so popular?

- Caudals are not technically difficult
  - Favorable anatomy
- Caudal vs. General Anesthesia
- Children are hemodynamically stable following a caudal
- Low complication rates.

Wellborn, Rice, Hannallah. Anesthes 1990; 72: 838-842
Watcha, Thach, Gunter. Anesthes 1989; 71: 613-615
Giafre, Dalens, Gombert. Anesth Analg 1996; 83:904-912

Caudals are popular, however…

- Bupivicaine alone often does not provide long enough analgesia
- Benefits to prolonging analgesia without placing an epidural catheter?
- How about adding opiods to the single shot bupivicaine caudal?

Why *not* use opiods?

- Opiods have been tried with unsatisfactory results:
- Morphine:
  - Adverse effects occur in children over 50% of the time: pruritus, nausea, vomiting, urinary retention, and respiratory depression.
  - Patients receiving neuroaxial administration of morphine are not eligible for day surgery.
- Fentanyl:
  - Does not prolong postoperative analgesia
- Alternatives to opiods as adjuvants?

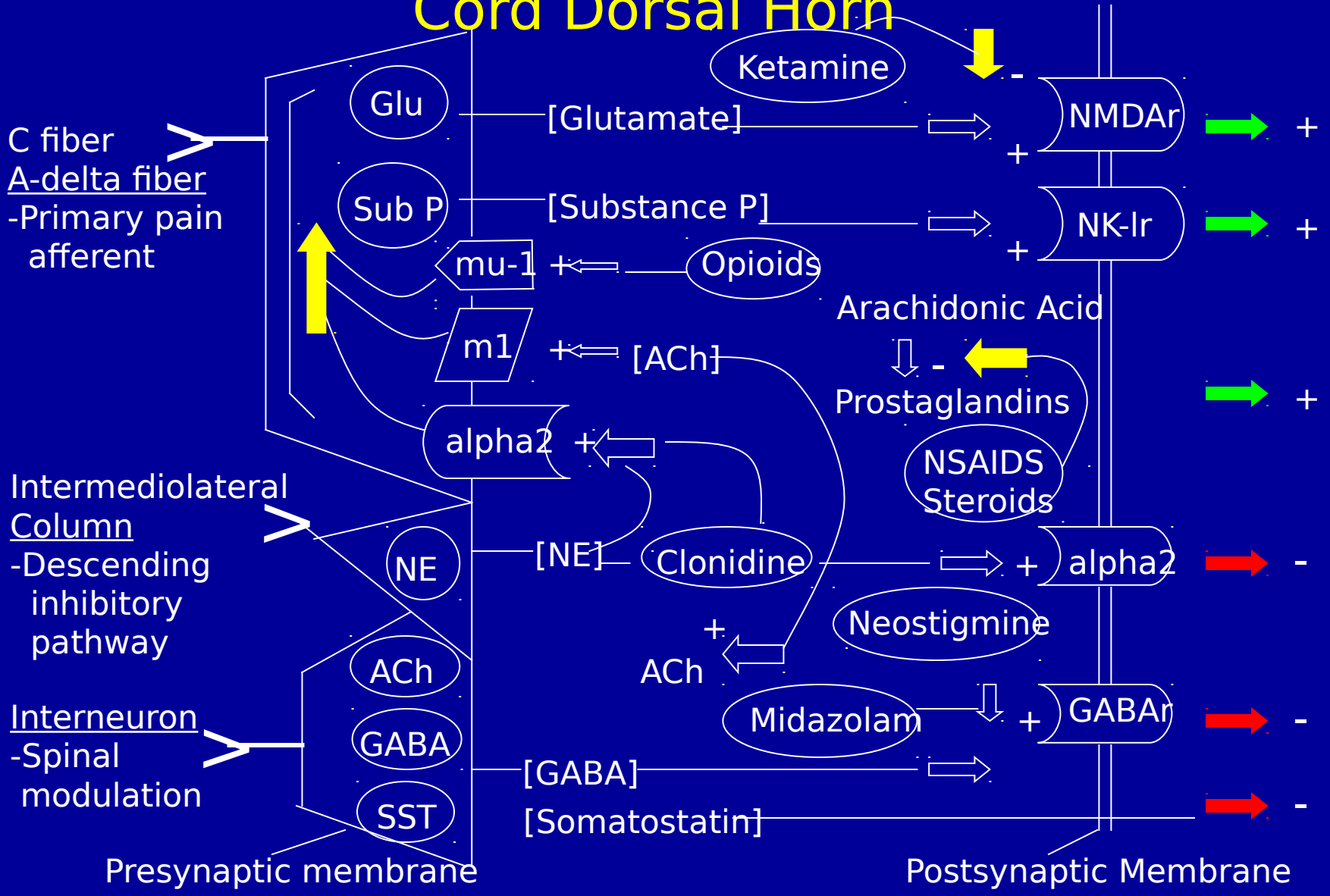
Dalens, Chrysotome. Paediatric Anaesth 1992; 1: 107
Dalens, Mansoor. Curr Opin Anaesthesiol 1994; 7:257
Mulroy. Reg Anesth 1996; 21: 89

- Warning in Miller, pg 1553

Off label, off label, off label…

- What I will be covering:
  - Non-opiod adjuvants to local anesthetics in the epidural space
  - Why they work
  - What we know, and don’t know about side effects and toxicities

Nociceptive Pathway and Action of Intrathecal Analgesic Agents in the Spinal Cord Dorsal Horn



Hodgson et al. A & A 1999;88:797-809

WRAMC, yesterday's medicine... tomorrow.

Not true with clonidine!

Site of action:

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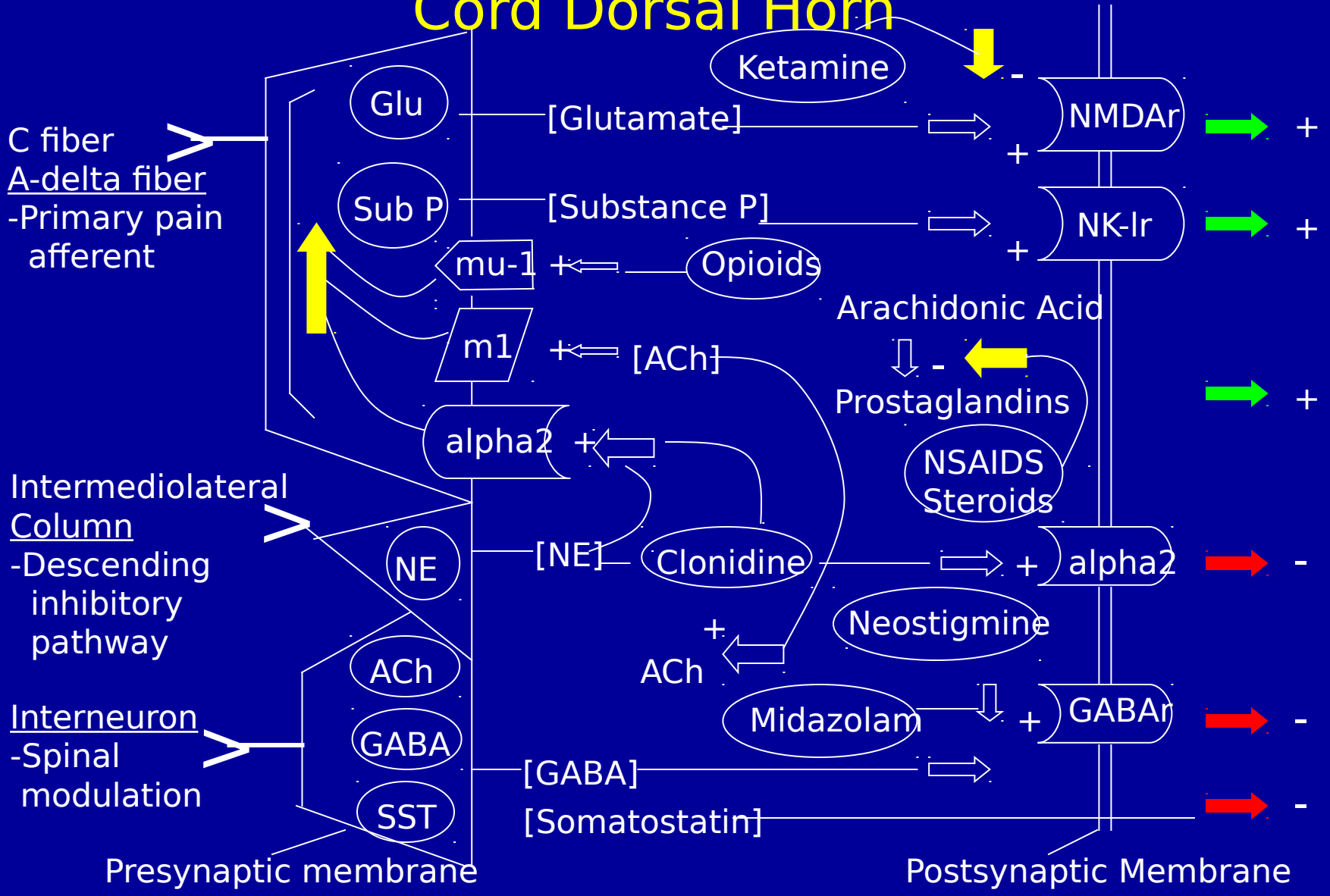


Hodgson et al. A & A 1999;88:797-809

Clonidine (cont'd)…

- Mechanism of action
  - Pain activates intrinsic descending inhibitory pain pathways→ increase of NE in the CSF→Increases Ach levels and acts as an alpha-2 agonist→ reduces the release of substance P
  - Clonidine stimulates release of NE plus interacts with pre and postsynaptic alpha-2 receptors in the dorsal horn of the spinal column

-Eisenach JC, Detweiler DJ, Tong C. Anesth Analg 1996; 82: 621-626
-Klimsena et al. Anesthesiology 1997; 87: 110-116

Clonidine (cont'd)

- Evidence for site of action:
  - Epidural vs. IV/IM administration of equal doses of clonidine
  - Autoradiographic localization of alpha-2 adrenoreceptors in spinal cord of sheep
  - Pharmacological antagonism in the CSF

-Bonnet F, Boico O, Rostaing S., Anesthesiology 1990; 72: 423-427
-Klimaha W, Ilong C, Eisanach JC. Anesthesiology 1997; 87 110-116
-Tyce GM, Yaksh TL. J Physiology 1981; 314: 513-529

Clonidine (cont'd)

- Summary of evidence:
  - Most extensively studied non-opiod additive
  - Consistently prolongs analgesia of caudals by 2-3 hours (doubles what analgesia bupivicaine provides alone)
  - Decrease in shivering, vomiting, agitation.

-Ansermino M, Basu R, Vandebeek C, Montgomery C. Paed Anaes 2003; 13: 561-573
-Bock M, Kunz P, Schreckenberger R. Br J Anaesth 2002; 88: 790-796
-Kulka PJ, Bressem M, Tryba M. Anesth Analg 2001; 93: 335-338
-Sia S. Br J Anaesth 1998; 81: 145-146
-Motsch J, Bottiger BW, Bach A. Acta Anaesthesiol Scand 1997;41: 877-883

Clonidine (cont'd)

- Side effects:
  - No prolongation of motor blockade
  - No increase in desaturations/apnea
  - Sedation (benefit?)
  - Cardiovascularly stable in pediatric population.

-Constant I, Gall O, Gouyet L, Chauvin M, Murat I. Br J Anaesth 1998; 80(3): 294-298
-Motsch J, Bottiger BW, Bach A, et al. Acta Anaesth Scand 1997; 41(7): 877-883
-Ivani G, De Negri P, Conio A, Amati M, Roero S, et al. Acta Anaesth Scand 2000; 44(4): 446-44

Clonidine (Cont'd)

- Neurohistopathological evidence:
  - No toxicity in animal studies
  - Extensive exposure to humans since 1984 with no clinical evidence of neurotoxicity.

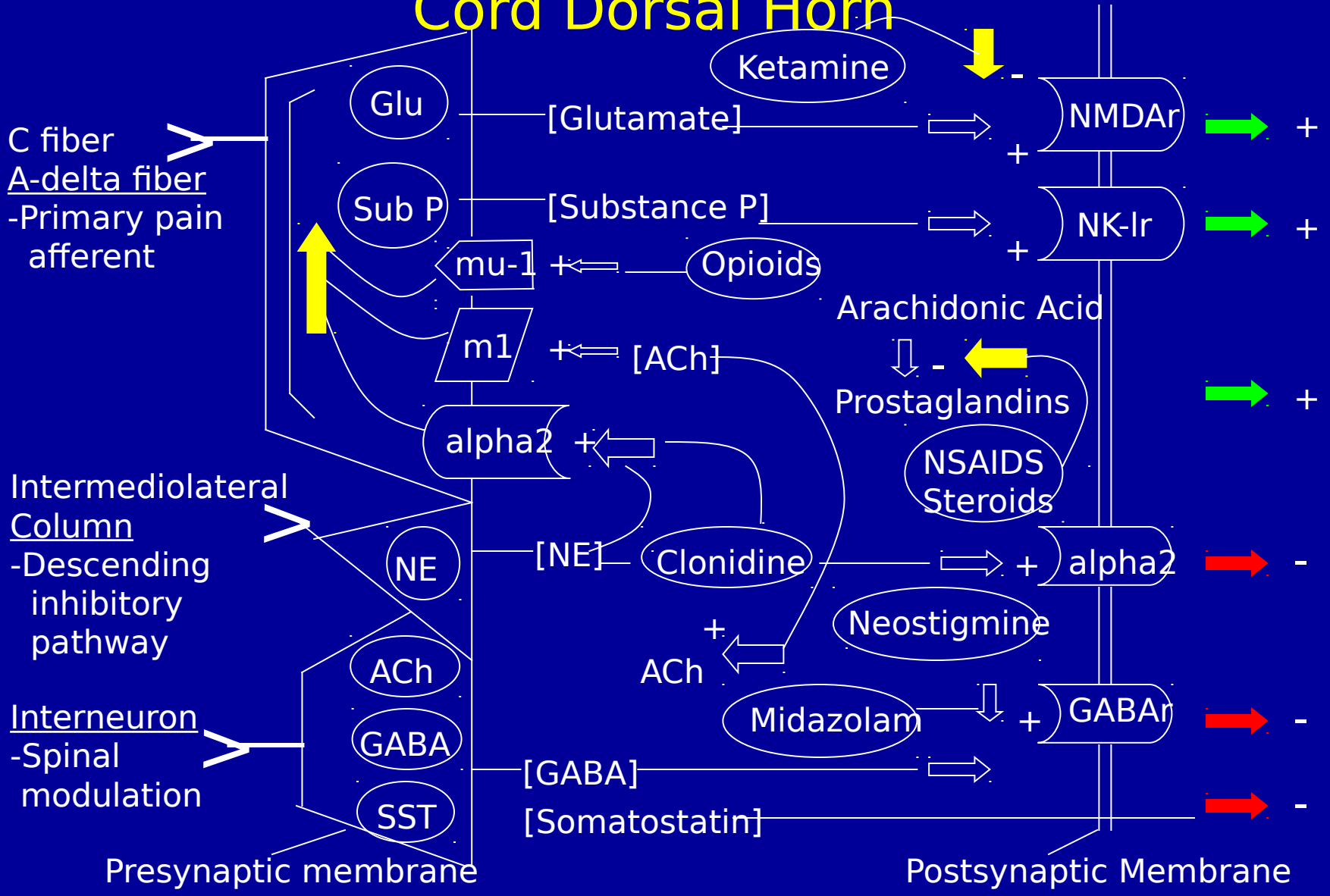
-Eisenach JC, De Kock M, Klimscha W. Anesthesiology 1996; 85: 655-674
-Hodgson P, Neal J, Pollock J, Liu S. Anesth Analg 1999; 88: 797-808

Ketamine:

- Site of Action:
  - Studies comparing IV and IM ketamine to caudally administered ketamine.
  - Proposed Receptors:
    - NMDA antagonism, mu-receptor agonism, and voltage sensitive Na channel interaction

-Martindale, Dix, Stoddart. British J Anesth 2004; 92(3): 344-347
-Smith DJ, Bouchal RL, de Sanctis RA. Neuropharmacology 1987; 26: 1253-1260
-Hirota K, Lambert DG. Br J Anaesth. 1996; 77: 441-444
-Brau ME, Sander F, Vogel W. Anesthesiology1997; 86: 394-404

Nociceptive Pathway and Action of Intrathecal Analgesic Agents in the Spinal Cord Dorsal Horn



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Ketamine:

- Evidence:
  - 5 studies looking at caudal use of ketamine combined with bupivicaine compared to bupivicaine alone.
    - Compared to local alone, addition of 0.25 mg/kg to 0.5 mg/kg significantly prolonged analgesic effects of the caudal
    - Dose related side effects were observed

-Naguib M, Sharif AM, Seraj M. Br J Anaesth 1991; 67:550-564
-Cook B, Grubb DJ, Aldridge LA. Br J Anaetsth 1995; 75: 698-701
-De Negri P, Ivani G, Visconti C.Paed Anasth 2001; 11: 679-683
-Ansermino M, Rahul B, Vandebeek C, Montgomer C. Paed Anaes 2003; 13: 561-573
-Weber F, Hinnerk W. Paediatric Anaesthesia 2003; 13: 244-248

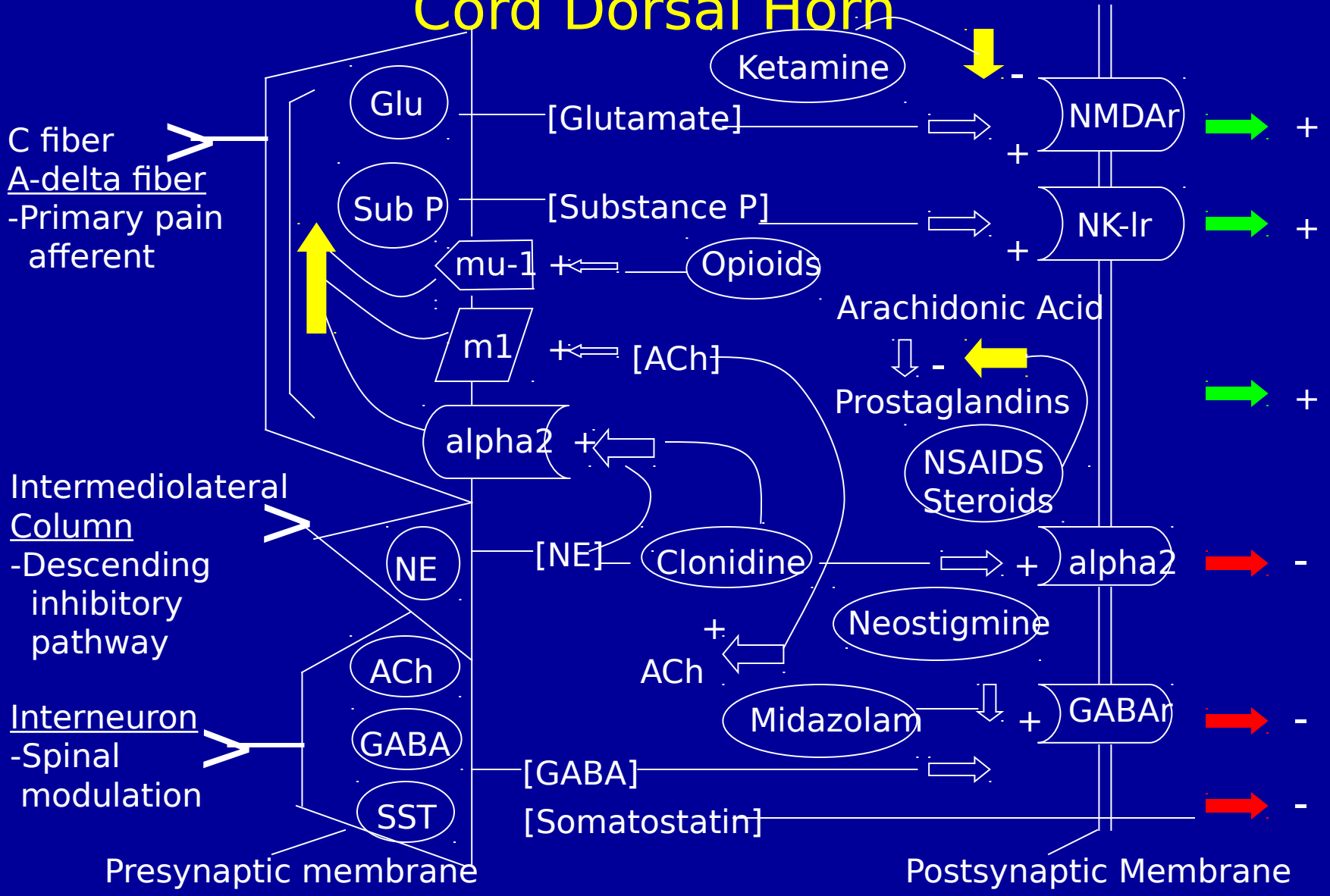
Ketamine (cont'd)

- Toxicity
  - Advantages of preservative free S(+)-ketamine
  - Animal studies
  - Inadvertent intravascular injection
    - Doses studied have been 0.25 to 1 mg/kg

-Hodgen, Neal, Pollock, Liu. Anesth Analg 1999; 88: 797-809
-Borgbjerg FM, Svensson BA, Frigast C. Anesth Analg 1994; 79: 105-111

Neostigmine
(not just for reversal anymore...)

Nociceptive Pathway and Action of Intrathecal Analgesic Agents in the Spinal Cord Dorsal Horn



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Neostigmine (cont'd)

- Studies to support site of action:
  - CSF studies
  - Radiographic evidence
  - Pharmacological antagonism in the caudal space

-Lauretti GR, Reis MP, Prado WA. Anes Analg 1996; 82: 1182-1187
-Yoon MH, Yoo KY, Jeong CY. J Korean Med Sci 2001; 16:498-504
-Naguib M, Yaksch TL. Anes 1994; 80: 1338-1348

Neostigmine (cont'd)

- Effect:
  - Dose related analgesia
- Evidence:
  - Studied in India:
    - Double-blind prospective randomized trial of 120 children undergoing hypospadius repair.
    - Staged dosing with 10, 20, 30, 40, 50 mcg/kg of neostigmine alone.
    - Up to 6.5 hour interval with no rescue opiod needed with no significant increase in N/V.

Batra, Arya, Mahajan, Chari. Paed Anaes 20003; 13: 515-521

Neostigmine (cont'd)

- Side Effects:
  - Increased NV in dose-dependent manner when combined with GA compared to GA alone.
  - Increase in urinary retention which was brief compared to opiods
  - No increase in motor weakness, respiratory depression, pruritis, HR changes compared to opiods

-Batra et al. Paed Anaes 2003; 13: 515-521
-Yoon, Choi, Kwak. Anes Anal 2004; 98: 1374-1379
-Hood DD, Eisenach JC, Tuttle R. Anesth 1995; 82: 336-343

Neostigmine (cont'd)

- Toxicity:
  - No signs of neurotoxicity in sheep, dogs, and rats
    - Preserved spinal blood flow and no changes in histopathology
  - Human safety studies are underway with no evidence of clinical signs of neurotoxicity

-Yaksh TL, Grafe MR, Malkmus S. Anesthes 1995; 82: 412-417
-Hood DD, Eisenach JC, Tong C. Anesthes 1995; 82: 428-435

Midazolam

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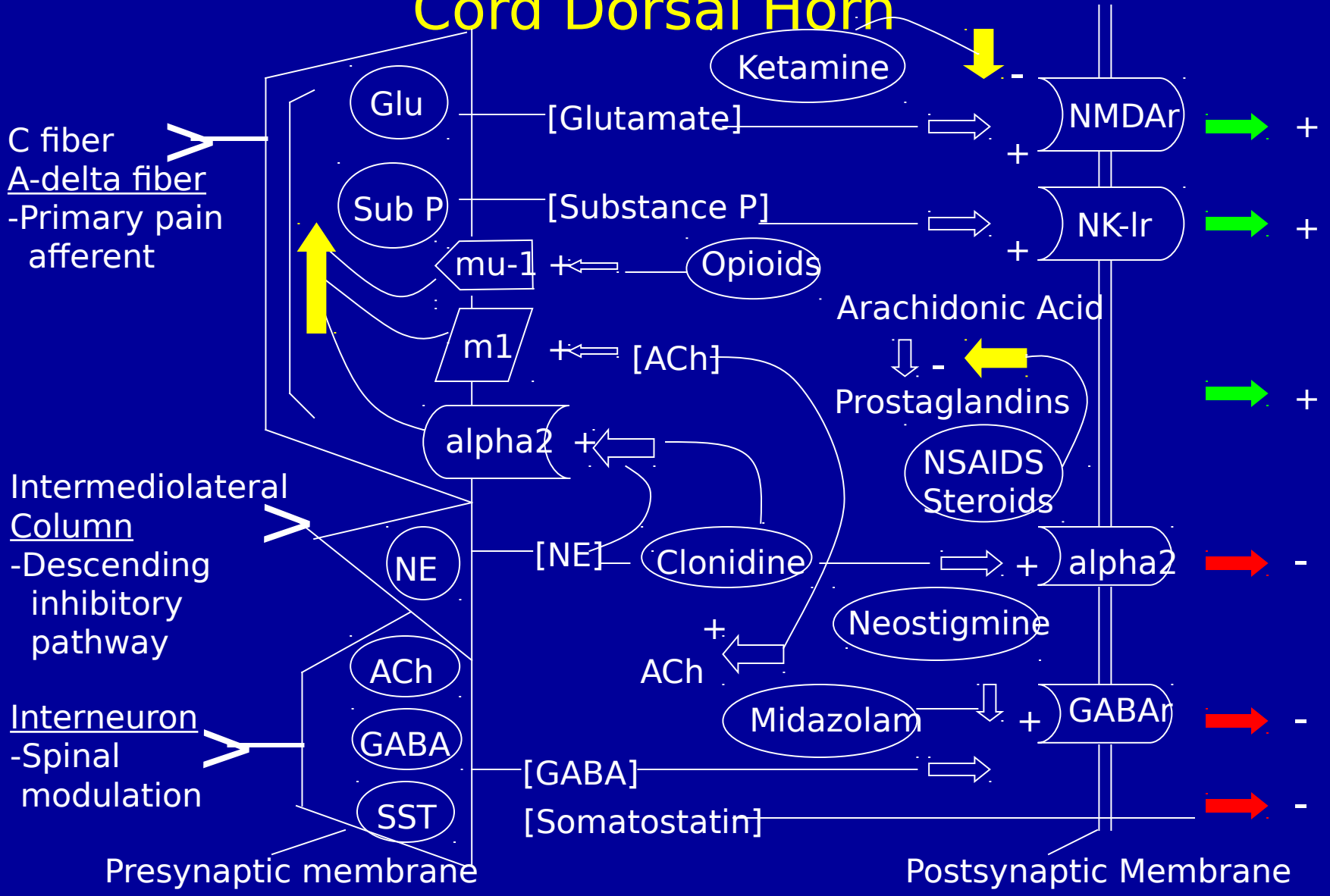

Hodgson et al. A & A 1999;88:797-809

Midazolam (cont'd)

- Mechanism:
  - GABA receptors and role in nociception
  - Pharmacological antagonism as evidence for site of action

-Crawford ME, Jensen FM, Tofidahi DB. Br J Anaesth 1993; 70: 642-646
-Nishiyama T, Matsukawa T, Hanaoka K. Acta Anaesth Scand 1999; 43: 568-572

Midazolam (cont'd)

- Benefits:
  - Few studies at this time…however:
    - Appears to be synergistic with bupivicaine in prolonging analgesia.
    - No increase in sedation beyond the first hour.

-Naguib M, el Gammal M, Elhattab YS. Can J Anaesth 1995; 42: 758-764
-Mahagan R, Batra YK, Grover VK. Int J Clin Pharmacol Ther 2001;39: 116-120

Midazolam (cont'd)

- Toxicity:
  - Conflicting results in animal studies
    - Initial studies showed no negative effects
    - 2 subsequent studies showed negative effects
      - However…
  - Human studies:
    - Case reports of prolonged intrathecal use showed no negative effects

-Ansermino M et al. Paediatric Anaesth 2003; 13: 561-573
-Malinovsky JM, Gozian A, Lepage JY. Anesth 1991; 75: 91-97
-Svensson , Welin M, Gordh T Jr, Westman J. Regional Anes 1995; 20: 426-434
-Borg PA, Krijen HJ. Clin J Pain 1996; 12: 63-68

Adenosine

Adenosine (cont'd)

- Mechanism
  - Presence of alpha-1 and alpha-2 subtype receptors on the spinal cord
    - Presynaptic effects
    - Postsynaptic effects
  - Pharmacological antagonism supports proposed method of action

-Sjolund KF, Solleri A, Segerdahl M, Lundeberg T. Anes Analg 1997; 85: 627-632
-Delander GE, Wahl JJ. J Pharmacal Exp Ther 1988; 246: 565-70
-Braas KM, Newby AC, Wilson VS, Snydei SM. J Neurosci 1986; 6: 1952-1961
-Choca JI, Green RD, Proudfit HK. J Pharmcol Exp Ther 1988; 247; 757-764
-Chiari A, Eisenach JC. Anesthes 1999; 90(5): 1413-1421

Adenosine (cont'd)

- Benefits:
  - Rat studies using adenosine alone and in combination with neostigmine or clonidine
  - Human studies using intrathecally administered adenosine

-Chiari et al. Anesthes 1999; 90(5): 1413-1421
-Rane K, Segerdahl M, Goiny M, Solleri A. Anesthes 1998; 89: 1108-1115

Adenosine (cont'd)

- Toxicity:
  - Neurotoxicity studies in Sweden:
    - Phase I Clinical Safety Trials have shown no adverse clinical neurotoxic effects of intrathecally administered adenosine.

-Rane K, SegerdahlM, Goiny M, Solleri A. Anesthes 1998; 89: 1108-1115

Gabapentin

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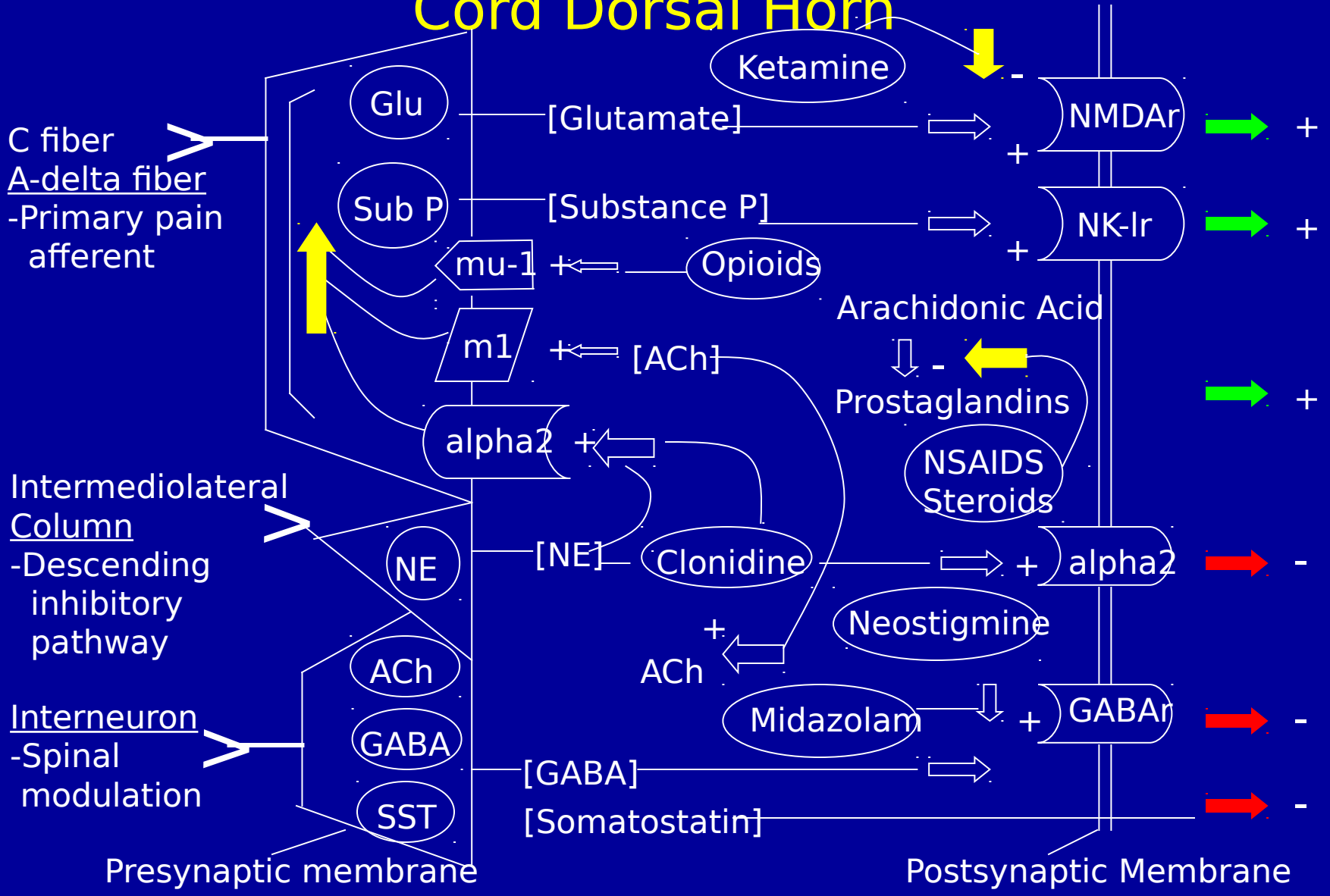

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Gabapentin (cont'd)

- Much is unknown at this point…
  - Site of action?
  - What receptors?
    - Intrathecal GABA antagonists vs. systemically administered gabapentin
    - Intrathecally administered D-Serine (NMDA agonist) vs. intrathecally administered gabapentin
    - Muscarinic, adenosine, calcium channels, and opiod receptors are also suspected to be involved

-Choi JJ, Jeong SW. J Korean Med Sci 2003; 18: 467-474
-Field MJ, Holloman EF, McCleary S. J Pharmacol ExpTher 1997; 282: 1242-1246

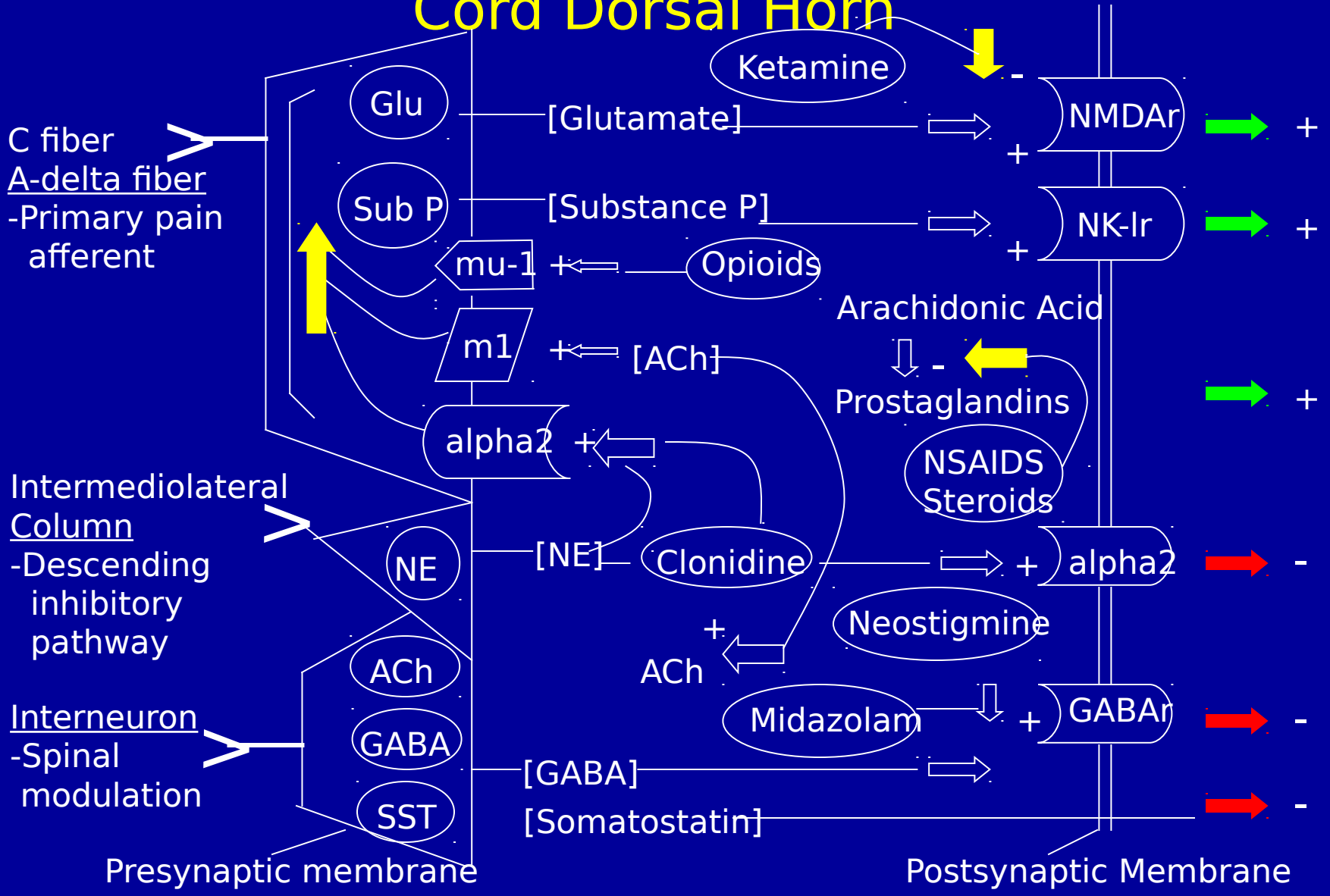
Gabapentin (cont'd)

- What is known:
  - Benefits have been shown in animal studies
    - Pain model in rats
- What is not known: toxicity
  - Not well studied/documented

-Yoon MH, Choi JI, Kwak SH. Anes Analg 2004; 98:1374-1379

NSAID’s

Nociceptive Pathway and Action of Intrathecal Analgesic Agents in the Spinal Cord Dorsal Horn



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NSAID's

- What has been studied:
  - Prostaglandins and their involvement in the spinal cord
  - Ketorolac and lysine acetylsalicylic acid (L-ASA)
    - Analgesic efficacy seen in rats

-Malmberg AB, Yaksh TL. Anesthes 1993; 79: 270-281
-Amiot JF, Palacci JH, Vedrenne C, Pellerin M. Ann Fr Anesth Reanim 1986; 5: 462

NSAID's (cont'd)

- Toxic effects:
  - Ketorolac has not been studied for neurotoxicities yet
  - L-ASA has mixed results:
    - One study showed no neurohistopathologic effects in rats
    - One study showed radicular demyelination injury in 1/7 rats

-Svensson BA, Kailsten R, Kristensen JD. Acta Anaesthesiol Scand 1993; 37: 799-805
-Amiot et al. Ann Fr Anesth Reanim 1986; 5: 462

After hearing the evidence...

Are you prepared to abandon the use of bupivicaine altogether?

When bupivicaine is not your friend…

- Risk of inadvertent intravascular injection
  - Rare (less than 1:2000). Can be lethal.
- Unreliable intravascular markers
- Is it possible to use purely non local anesthetics or opiods for caudals…?

Desparmet, Mateo, Scoffey. Anesthesiology 1990; 72: 245-251
Liu. Anesth Analg 1996; 83: 97=101
Fisher, Shaffner, Yaster. Can J Anaesth 1997;44: 592-598

When adjuvants are used as primary agents:

- Clonidine plus S(+)-Ketamine (No local!)
  - Caudals for inguinal hernia repair
  - 3 groups:
    - 1 mg/kg S(+)-ketamine
    - 1 mg/kg S(+)- ketamine plus 1mcg/kg clonidine
    - 1 mg/kg S(+)- ketamine plus 2 mcg/kg clonidine
  - Mean period of analgesia: 23 hours in clonidine groups vs. 13 hours with ketamine

Hager, Marhofer, Sitzwohl, Adler, Kettner, Semsroth. Anesth Analg 2002; 94: 1169-1172

COMBINATIONS CONT'D:

- Neostigmine and Clonidine:
  - Rat models showed synergism
  - Possible mechanisms of synergism
- Benefits of not using local anesthetics:
  - Avoid toxicity of local anesthetics
  - Inadvertent intravascular injection is of little consequence: 1-3 mcg/kg clonidine with 10-30 mcg/kg neostigmine...(have your atropine ready!)

Yoon, Yoo, Jeong. J Korean Med Sci 2001; 16: 498-504

Conclusion

- Limitations of studies
- How to apply the information
  - Many questions left unanswered…